US 20210277371A1

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2021/0277371 A1

RAN et al. (43) Pub. Date: Sep. 9, 2021

(54) **ENGINEERING OF SYSTEMS, METHODS AND OPTIMIZED GUIDE COMPOSITIONS WITH NEW ARCHITECTURES FOR SEQUENCE MANIPULATION**

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(21) Appl. No.: **17/123,918**

(22) Filed: **Dec. 16, 2020**

Related U.S. Application Data

(63) Continuation of application No. 15/172,636, filed on Jun. 3, 2016, now abandoned, which is a continuation-in-part of application No. PCT/US2014/070152, filed on Dec. 12, 2014.

(60) Provisional application No. 61/939,256, filed on Feb. 12, 2014, provisional application No. 61/915,267, filed on Dec. 12, 2013.

Publication Classification

(51) **Int. Cl.**

C12N 9/22	(2006.01)
C12N 15/63	(2006.01)
C12N 15/113	(2006.01)
C12N 15/115	(2006.01)
C12N 15/90	(2006.01)

(52) **U.S. Cl.**

CPC ***C12N 9/22*** (2013.01); ***C12N 15/63*** (2013.01); ***C12N 15/113*** (2013.01); ***C12N 15/115*** (2013.01); *C12N 2310/20* (2017.05); ***C12Y 301/00*** (2013.01); *C12N 2310/16* (2013.01); *C12N 2310/3519* (2013.01); *C12N 2310/10* (2013.01); ***C12N 15/907*** (2013.01)

(57) **ABSTRACT**

The invention provides for systems, methods, and compositions for altering expression of target gene sequences and related gene products. Provided are structural information on the Cas protein of the CRISPR-Cas system, use of this information in generating modified components of the CRISPR complex, vectors and vector systems which encode one or more components or modified components of a CRISPR complex, as well as methods for the design and use of such vectors and components. Also provided are methods of directing CRISPR complex formation in eukaryotic cells and methods for utilizing the CRISPR-Cas system. In particular the present invention comprehends optimized functional CRISPR-Cas enzyme systems. In particular the present invention comprehends engineered new guide architectures to be used in optimized CRISPR-Cas enzyme systems.

Specification includes a Sequence Listing.